ARTJEN COMPLEXUS INC.

January 5, 2005

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Office of Nutritional Products
Labeling and Dietary Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740
Attention: Victoria Lutwak

Re: ArtJen's *New Dietary Ingredient Notification* for α-cyclodextrin
Dated December 1, 2004

Dear Dr. Levy:

Further to the above referenced submission we would like to offer this addendum. Please find attached an original and two copies of a response from the Department of Health and Human Services Food and Drug Administration to Diane McColl, acting on behalf of Wacker Biochemical Corporation, regarding Wacker's GRAS notification for α-cyclodextrin. It is this same material that our above referenced *Notification* pertains to. As the Department of Health and Human Services Food and Drug Administration *has no questions at this time regarding Wacker's conclusion that alpha-cyclodextrin is GRAS under the intended conditions of use.*, we feel that this is strong support for our conclusions that α-cyclodextrin is safe for human consumption as a dietary supplement to, at least, our recommended levels of six grams per day. Please note that Wacker's conclusions are that α-cyclodextrin is GRAS as a food additive to approximately three times our suggested level.

We would appreciate your kind consideration of this document as part of our *Notification.*

Thank you and we look forward to a positive response from your office.

Sincerely,

Joseph D. Artiss, Ph.D., FACB
Vice President

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Food and Drug Administration
College Park, MD 20740

Diane McColl
Hyman, Phelps & McNamara, P.C.
700 Thirteenth Street, N.W.
Suite 1200
Washington, D.C. 20005-5929

Re: GRAS Notice No. GRN 000155

Dear Ms. McColl:

The Food and Drug Administration (FDA) is responding to the notice, dated June 25, 2004, that you submitted on behalf of Wacker Chemical Corporation (Wacker) in accordance with the agency's proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal). FDA received the notice on June 28, 2004, filed it on June 30, 2004, and designated it as GRAS Notice No. GRN 000155.

The subject of the notice is alpha-cyclodextrin. The notice informs FDA of the view of Wacker that alpha-cyclodextrin is GRAS, through scientific procedures, for use in selected foods for fiber supplementation, as a carrier or stabilizer for flavors (flavor adjuvant), colors, vitamins and fatty acids, and to improve mouth-feel in beverages. These uses are described in Table 1.

Table 1
Food categories and use levels for alpha-cyclodextrin

Food category	Maximum use level percent (w/w)
Breads, rolls, cakes, baking mixes, refrigerated dough	5
Brownies and bars	7
Crackers (sweet and non-sweet)	10
Diet soft drinks, beverage mixes, fruit juices, instant coffees and teas, coffee whiteners (dry), formula diets, meal replacements, and nutritional supplements	1
Vegetable juices, soy milk and non-soy (imitation) milk	2
Ready-to-eat breakfast cereals	2 to 9*
Instant rice, pasta, and noodles (prepared)	2
Condiments	3

Reduced fat spreads	20
Dressings and mayonnaise	5
Yogurt, milk beverage mixes, and frozen dairy desserts	2.5
Pudding mixes (dry)	1
Snack foods	1
Canned and dry soups (prepared)	2
Hard candy	15
Chewing gum	10

[a] The notifier states that use level in ready-to-eat cereals will vary based on weight of serving size (i.e., if less than 20 g/cup the level is 2 percent; 20-43 g/cup the level is 9 percent; greater than or equal to 43 g/cup the level is 5 percent).

As part of its notice, Wacker reports that a panel of individuals (Wacker's GRAS panel) has evaluated the data and information that are the basis for Wacker's GRAS determination. Wacker considers the members of its GRAS panel to be qualified by scientific training and experience to evaluate the safety of substances added to food. Wacker's GRAS panel report discusses the following information concerning alpha-cyclodextrin: 1) the manufacturing process and specifications; 2) estimated daily intake; 3) absorption, distribution, metabolism, and excretion; 4) published toxicological studies conducted in animals; 5) published studies that concern cellular and genetic effects; and 6) published studies conducted with humans. Wacker's GRAS panel concludes that, based on scientific procedures, alpha-cyclodextrin meeting appropriate food grade specifications and manufactured in accordance with current good manufacturing practices, is GRAS under the conditions of intended use.

The alpha-cyclodextrin is intended for use in selected solid, semi-liquid, and liquid foods. According to the notifier, alpha-cyclodextrin has nutritional properties similar to fermentable dietary fiber, is stable under food processing conditions, and has a low viscosity in aqueous solutions. Structurally, alpha-cyclodextrin is shaped like a hollow truncated cone or torus. The cavity of alpha-cyclodextrin is hydrophobic and the outer surface is hydrophilic. Alpha-cyclodextrin is water soluble and can form inclusion complexes with lipophilic substances. The formation of reversible inclusion complexes is the basis for alpha-cyclodextrin applications.

Alpha-cyclodextrin (CAS Registry No. 10016-20-3), also known as cyclohexa-amylose, cyclomalto-hexose or alpha-dextrin, has an empirical formula of $(C_6H_{10}O_5)_6$ and molecular weight of 973 Daltons. Structurally, alpha-cyclodextrin is a cyclic polymer of six alpha-1,4-linked glycopyranosyl units.

The notifier describes their manufacturing process for alpha-cyclodextrin. In the first step of alpha-cyclodextrin production, food-grade, liquefied starch is treated with a cyclodextringlycosyltransferase (CGTase, EC 2.4.1.19, CAS 9030-09-5) under controlled pH and temperature conditions. The CGTase is obtained from a recombinant strain of *Escherichia*

coli K12, harboring the CGTase gene of *Klebsiella oxytoca*. Alpha-cyclodextrin is precipitated from the enzymatic reaction mixture by addition of 1-decanol. The precipitate is further purified by dissolution in water and re-precipitation. The 1-decanol is separated from alpha-cyclodextrin by decantation and steam distillation. The final alpha-cyclodextrin product is obtained by crystallization and is a white powder with a purity of ≥ 98.0 percent. The notifier provides additional specifications including limits on the maximum levels of volatile organic compounds, heavy metals, and lead (less than 0.5 parts per million[1]).

Using the foods and use levels summarized in Table 1 and the two day consumption data from the United States Department of Agriculture (USDA) Continuing Survey of Food Intakes by Individuals 1994-96, 98 (CSFII), the notifier calculated an estimate of the daily intake (EDI) of alpha-cyclodextrin. The notifier estimates the mean and 90th percentile intake (users only and of all age groups combined) of alpha-cyclodextrin from the intended uses in Table 1 (except chewing gum) to be 11.4 and 19.8 g/person/day. The calculation also includes a mean "per eating occasion" intake of 3.9 g/person. The notifier used a separate survey on chewing gum use in the United States to provide an additional EDI for alpha-cyclodextrin ingested from chewing gum as 0.9 g/person/day.

The notifier reports that the Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated alpha-cyclodextrin in June 2001 for technological uses in food. On the basis of the available safety studies on alpha-cyclodextrin and studies on the related beta- and gamma-cyclodextrin, JECFA allocated an Acceptable Daily Intake (ADI) of "not specified"[2] for alpha-cyclodextrin. The notifier reports that the 63rd meeting of JECFA in 2004 also determined an ADI of "not specified" for alpha-cyclodextrin.

Wacker's GRAS panel discusses published studies regarding absorption, distribution, metabolism, excretion, bioavailability, toxicity and mutagenicity conducted with alpha-cyclodextrin in humans and various animal species. In summary, alpha-cyclodextrin is not digested by the mammalian digestive enzymes; however, it is completely fermented by the intestinal microbiota. Less than 1 percent of the alpha-cyclodextrin is absorbed; however, this amount is not metabolized and is excreted unchanged in the urine. Two 13-week toxicity studies with rats and dogs provide no evidence for adverse reactions in the gastrointestinal-tract, the kidneys, the liver or any other organs or tissues at alpha-cyclodextrin intakes of up to 20 percent of the diet (13 g/kg bw/day in rats and 10 g/kg bw/day in dogs). The notifier states that the EDI calculations indicate that the intake of alpha-cyclodextrin per eating occasion (3.9 g/person)

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[1] The lead specification is a maximum level of 0.5 ppm; however, batch analysis records included in GRN 000155 indicate a lead level of less than 1 ppm. FDA notes that a maximum lead level of 1 ppm is within the specifications described in the Food Chemicals Codex (5th edition) for beta- and gamma-cyclodextrin.

[2] ADI 'not specified' is used to refer to a food substance of very low toxicity which, on the basis of the available data (chemical, biochemical, toxicological and other) and the total dietary intake of the substance arising from its use at the levels necessary to achieve the desired effects and from its acceptable background levels in food, does not, in the opinion of the Committee, represent a hazard to health. For that reason, and for the reasons stated in the individual evaluations, the establishment of an ADI expressed in numerical form is not deemed necessary. An additive meeting this criterion must be used within the bounds of good manufacturing practice, i.e. it should be technologically efficacious and should be used at the lowest level necessary to achieve this effect, it should not conceal food of inferior quality or adulterated food, and it should not create a nutritional imbalance.

would be below the doses that were tolerated by adult volunteers who experienced no side-effects (10 g/person) or minimal intestinal symptoms (25 g/person). Based on these studies, the GRAS panel concludes that alpha-cyclodextrin is safe for its intended uses.

Based on the information provided by Wacker, as well as other information available to FDA, the agency has no questions at this time regarding Wacker's conclusion that alpha-cyclodextrin is GRAS under the intended conditions of use. The agency has not, however, made its own determination regarding the GRAS status of the subject use of alpha-cyclodextrin. As always, it is the continuing responsibility of Wacker to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.

In accordance with proposed 21 CFR 170.36(f), a copy of the text of this letter, as well as a copy of the information in the notice that conforms to the information in proposed 21 CFR 170.36(c)(1), is available for public review and copying on the homepage of the Office of Food Additive Safety (on the Internet at http://www.cfsan.fda.gov/~lrd/foodadd.html).

Sincerely,

Patricia Mathes for LMT

Laura M. Tarantino, Ph.D.
Director
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition